“Growing Your White Blood Cells to Treat Your Cancer” (Matthew Dons) [#79]

Brad Power
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“When you think about the cancer, you've got your immune system, and cancer does immunosuppression. That means it generally weakens your immune system, particularly the number of white blood cells produced.” – Matthew Dons

“I strongly, strongly believe that I'm alive because of multiple treatments, especially multiple treatments at the same time, and especially choosing treatments that are not going to trash my immune system too much.” – Matthew Dons

“The standard care in Japan is much higher for cancer. It's probably just a few years ahead of the US, but maybe 10 years ahead of the UK.’ – Matthew Dons

Meeting Summary

Among the treatment options that advanced cancer patients may consider, immunotherapies have the major advantage that they can lead to very durable responses (a “cure”), while most other therapies work for a while, then fail. Cancer treatments tend to be toxic or invasive. Sadly, they are often ineffective. Immunotherapies have many advantages, but they are newer than traditional treatments like surgery or chemotherapy, so are harder to access. An international search, including Japan, can uncover more treatment options and more access, especially to immunotherapies.

Matthew Dons, Director of Make Cancer History, is uniquely qualified to talk about a global search for cancer treatments, and especially immunotherapies. When he was diagnosed with stage IV (metastatic) colon cancer in 2016 at the age of 36, it seemed unlikely he’d live more than a year. Seven years later he’s still doing well, thanks to a treatment based around boosting his immune system by growing his own white blood cells. Matthew is neither a doctor nor a researcher; he is an example of what we call a “super patient”. (See for example our discussion with super patient Mark Taylor here.) He has studied immunotherapies extensively to guide his own care, and he has advised many patients around the world about how to access such therapies. Over the years he has developed some distinctive ideas about what works and what doesn’t.

Why should you consider growing your white blood cells to treat your cancer?

Immunotherapies (a treatment leveraging your immune system), such as growing your white blood cells to treat your cancer, offer one of the best paths to a durable response -- they are fighting a biological system (your cancer) with another system (your immune system), rather than the hit-and-miss, less durable approach of targeting a biomarker with a single drug or poisoning your cancer with chemotherapy. Certain immunotherapies offer a treatment option to nearly every cancer patient because they are neither targeted to a specific “tissue of origin”, like

lung cancer or colon cancer, nor are they targeted to a biomarker, a protein that your cancer cells overexpress, like BRCA or EGFR.

The medical term for growing your white blood cells to treat your cancer – autologous adoptive cell transfer – is a mouthful of medical jargon. Let’s break it down:

- *Autologous*: using your cells to treat your disease, a Latin term meaning “from your body”
- *Adoptive cell transfer*: taking your healthy cells, e.g., white blood cells, growing them in a lab, then putting them back into your blood
- *Apheresis*: the name for the process that takes your blood, runs it through a machine to separate out one or more constituents, and returns the remainder back to you

For example, in the treatment Matthew Dons has received in Japan, he’s gotten a huge number of extra white blood cells of various types (T-cells, NK cells, and dendritic cells) that were taken from him using apheresis, then grown in a lab, then reinfused into him. Another example is an autologous dendritic cell therapy called Provenge (Sipuleucel-T) for metastatic prostate cancer, which has shown a four-month increase in mean survival in clinical trials, and greater than one year in real world experience.

Growing your white blood cells is different from other immunotherapies you may have heard of and considered, such as (1) immune checkpoint inhibitors (e.g., Keytruda/pembrolizumab, OPDIVO/nivolumab), (2) CAR-T (chimeric antigen receptor T-cell) therapy, or (3) personalized neoantigen vaccines.

1. **Immune checkpoint inhibitors**: Immune checkpoints stop your immune system from attacking yourself. Immune checkpoint inhibitors remove these brakes on your immune system. Keytruda is one checkpoint inhibitor that was approved in the U.S. in 2016 for skin cancer. Then in 2017, it was approved in the U.S. for all tumor types and all cancer origins, if you have what's called “MSI high”, microsatellite instability high, which means your cancer is quite mutated. If you are an advanced cancer patient, checkpoint inhibitors are less likely to be effective because you have a very poor immune system, and removing the brakes generally won’t help. (For more on checkpoint inhibitors and MSI, please see our discussion with Heather Tomlinson, “How MSI and Other Tests Can Guide Immunotherapies for Cancer Treatment” here.)
2. **CAR-T cell therapy:** CAR-T cell therapy is also an adoptive cell transfer therapy, i.e., it is also putting T-cells, a type of white blood cell, into your blood. In the CAR-T process, they take a commercial cell line, and then genetically engineer T-cells to match the genetics of your cancer, which means they're very highly targeted. However, because they are engineered foreign cells (not autologous), your body has a high chance of reacting against the therapy. And the T-cells are only able to attack cancer cells that they recognize as cancer cells by an antigen or neoantigen label. (For more on CAR-T, please see our discussion with Andrew Rech, “Immunotherapy in Prostate Cancer - CAR-T and the Tumor Microenvironment” here.)
3. **Personalized cancer vaccines**: Personalized cancer vaccines can be used to introduce or stimulate selected T-cells to attack cancer cells. The vaccine is trying to get your body

> to produce enough of the right T-cells, and then combine it with things like checkpoint inhibitors or whatever makes sense to make sure that those T-cells can do their job and win the battle against your tumor. (For more on personalized cancer vaccines, please see our discussion with Willy Hoos, “Personalized Cancer Vaccines” here and with Lisa Butterfield, “Cancer Vaccines” here.)

By using three kinds of immune system white blood cells, Matthew Dons had a better chance of a response than these other immunotherapies. While T-cells need to recognize labels on the cancer cells, NK cells can attack cancer cells without labeling, while dendritic cells help identify and present antigens. NK cells can attack cells that are not labeled as cancer cells, are not presenting an antigen, or not labeled with a neoantigen. This is very important for late stage patients, because NK cells are able to attack cells that they recognize as being cancer, but not because of the labeling. As a late stage patient, many of the cancer cells that you have are these unlabeled ones. NK cells show good uptake in bones, even for late-stage cancer patients like Matthew Dons.

Why might you not want to consider growing your white blood cells to treat your cancer?

- **Hyper progression**: A theory in immunotherapy, citing patient experience. Immune system weakening and cancer's ability to evade immune responses are major factors in hyper progression.
- **Evidence**: NK cell therapies don’t have much clinical evidence.

What are principles for long-term survival from cancer?

1. **Access new treatments as quickly as possible**: Do not wait for the approval. If the science seems sound, and early results seem good – go for it.
2. **Combine treatments**: For example, combine immunotherapy and hyperthermia, which increases blood flow and enhances immune response.
3. **Get as much treatment as your body can take**: Choose a combination of gentler treatments.
4. **Choose treatments that cause less immune suppression**. For example, if you're going to have radiotherapy, find the one which causes the least bone marrow suppression.
5. **Choose clinics carefully:** Clinics should own their labs for quality control.

How can immunotherapies be enhanced?

- **Combine with targeted drugs**: For example, before your immunotherapy is administered, you can get a low dose of a targeted cancer drug (like cetuximab, which is used to treat advanced bowel cancer and head and neck cancers), which will mark the cancer cells, a bit like a neoantigen, making the cancer cells more visible to the T-cells.
- **Combine with radiofrequency ablation**: A minimally invasive procedure that shrinks the size of tumors procedure by the heat generated from medium frequency alternating current. It has been successfully applied in liver cancer before checkpoint inhibitors.
- **Combine with** high-intensity focused ultrasound. This is meant to be a drop-in replacement for radiotherapy, just like radiofrequency ablation was, to ablate the tumors.

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- **Condition dendritic cells for cancer treatment**: For example, promising results in primary brain cancer.
- **Combine with “cryoablation”:** (extreme cold) to freeze and kill abnormal cancerous and precancerous cells.
- **Inject therapies into the tumors**: The alternative the Japanese have come up with is to take dendritic cells and inject them in between your ribs because there's loads of lymph nodes there.
- **Condition with heat shock proteins**
- **Use the tumor tissue to condition the dendritic cells**
- **Analyze white blood cell activity in blood samples**
- **Get metronomic chemotherapy**: a low dose of chemotherapy given continuously, with no breaks

Why should you consider getting your immunotherapy in Japan?

- **Advanced treatments:** The standard care in Japan is very high for cancer. It's probably a few years ahead of the US, and maybe 10 years ahead of the UK.
- **Access**: Matthew Dons got his experience with immunotherapy in Japan, including tumor lysate-pulsed autologous dendritic cell therapy.
- **Low Cost**: Healthcare in Japan is far less expensive than in the US. It’s because of how the Japanese health system is regulated and with the buying power of Japan because there's a large, elderly population. For example, for Matthew Dons, the standard, intensive treatment was around $25,000.
- **Safety**: In Japan, medical mistakes are very rare. In the US, medical mistakes are the third biggest killer. When you are getting cancer treatment you are often looking at treatments that give you a few percent advantage over standard care. Medical mistakes eat away at that advantage.

What can you do to help with the global effort to cure cancer?

There’s no serious global effort to cure cancer. For some of the most deadly cancers, like colon cancer, which kills about one million people every year, some of the new drugs only add two months to your life. We’ll never have a cure for cancer with the current approach. We need something new. A new approach to treating cancer, focusing on “cancer agnostic” drugs and treatments is already getting great results in some countries.

Make Cancer History is a non-profit organization based in Tokyo with one aim: to cure cancer all over the world. That means helping scientists develop cheap, safe treatments that anybody can use. These treatments aren’t owned by any company, they are in the “public domain”, meaning any health system can use them without paying a license fee. With your help we can cure cancer and make it a thing of the past.

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Meeting Notes

SUMMARY KEYWORDS

treatment, cancer, cells, cancer cells, tumors, patient, immunotherapy, white blood cells, checkpoint inhibitors, japan, t cells, therapy, clinic, dendritic cells, nk cells, immune system, drug, brain cancer, chemo, doctor

SPEAKERS

Matthew Dons (91%), Brian McCloskey (4%), Roger Royse (3%), Amit Gattani (2%)

OUTLINE

1. Cancer treatment options with medical disclaimers. (0:02)
2. Immunotherapy in Japan for cancer treatment. (1:13)
3. Colon cancer treatment options with a personal story. (2:50)
4. Cancer treatment in Japan with a focus on immunotherapy. (7:09)
5. Cancer treatment using white blood cell therapy. (14:11)
6. Cancer immunotherapy and checkpoint inhibitors. (20:46)
7. Immunotherapy and cancer progression. (25:35)
8. Personalized immunotherapy for cancer treatment. (32:26)
9. Cancer treatment outcomes for patients with multiple treatments. (39:39)
10. Cancer treatment strategies with a focus on immunotherapy. (44:01)
11. Cancer treatment options and their effectiveness. (50:26)
12. Immunotherapy for cancer treatment in Japan. (57:49)

SUMMARY

- **Cancer treatment options with medical disclaimers.** 0:02
    - Brian McCloskey introduces the Cancer Patient Lab session, emphasizing the importance of consulting a doctor before pursuing any healthcare program.
- **Immunotherapy in Japan for cancer treatment.** 1:13
    - Matthew Dons shares his experience with immunotherapy in Japan, including a neoantigen peptide vaccine, which he has brought to the US for a fraction of the cost.
- **Colon cancer treatment options with a personal story.** 2:50
    - Matthew Dons shares his story of being diagnosed with stage 4 colon cancer in 2016 and how he found alternative treatment in Japan.
    - He was misled by poor survival rates in Europe.
- **Cancer treatment in Japan with a focus on immunotherapy.** 7:09
    - Matthew Dons: In Japan, medical mistakes are rare, giving an advantage in cancer treatment.
    - Matthew Dons explains adoptive cell transfer immunotherapy, different from checkpoint inhibitors like OPDIVO and Keytruda.
    - Matthew Dons discusses cancer agnostic treatment, explaining differences between tumor and tissue agnostic treatments.
- **Cancer treatment using white blood cell therapy.** 14:11

    - Matthew Dons discusses adoptive cell therapy for cancer treatment using white blood cells grown from the patient's own body.
    - Matthew Dons explains the process of fra CES, a blood separation technique, to a listener.
    - T cells and NK cells can attack cancer cells without labeling, while dendritic cells help identify and present antigens.
- **Cancer immunotherapy and checkpoint inhibitors.** 20:46
    - NK cells show good uptake in bones, even for late-stage cancer patients like Matthew Dons.
    - Matthew Dons explains the hyper progression theory in immunotherapy, citing patient experience.
- **Immunotherapy and cancer progression.** 25:35
    - Immune system weakening and cancer's ability to evade immune responses are major factors in hyper progression.
    - Matthew Dons explains pseudo progression in cancer treatment, a phenomenon where tumors appear to grow despite immunotherapy.
    - Researcher discusses using dendritic cells to target cancer cells through peptide-based immunotherapy.
- **Personalized immunotherapy for cancer treatment.** 32:26
    - Personalized cell processing for immunotherapy is crucial, with clinics owning their own labs for quality control.
    - Personalized cancer treatment can be improved through analysis of white blood cell activity in blood samples.
    - Explanation of how targeted drugs can enhance immunotherapy for cancer patients, with examples of drugs like Panitumumab and Cetuximab.
- **Cancer treatment outcomes for patients with multiple treatments.** 39:39
    - Researchers found promising results in treating cold tumors with radiofrequency ablation before checkpoint inhibitors in liver cancer patients.
    - Matthew Dons discusses cancer treatment options, including checkpoint inhibitors and combination therapies, and their effectiveness in different patient populations.
- **Cancer treatment strategies with a focus on immunotherapy.** 44:01
    - Matthew Dons emphasizes the importance of combining treatments, such as immunotherapy and hyperthermia, for optimal cancer treatment results.
    - Matthew Dons discusses hyperthermia therapy as a potential cancer treatment, highlighting its ability to increase blood flow and enhance immune response.
    - Matthew Dons advocates for combining multiple treatments to improve cancer survival chances, prioritizing gentler treatments with less immune suppression.
- **Cancer treatment options and their effectiveness.** 50:26
    - Matthew Dons discusses their experience with immunotherapy for cancer, including receiving treatment in Japan and experiencing a range of side effects.
    - Matthew Dons emphasizes the importance of considering the toll of international travel on the body when seeking treatment abroad.
    - Dr. Jones discusses using frozen tumor tissue to condition dendritic cells for cancer treatment, with promising results in primary brain cancer.
    - Matthew Dons emphasizes underutilization of RFA and cryoablation in cancer treatment.
- **Immunotherapy for cancer treatment in Japan.** 57:49
    - Matthew Dons discusses alternative cancer treatments, including high intensity focused ultrasound.

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- Dr. Ted Aneuma is a pioneer in immunotherapy in Japan, leading a clinic that uses metronomic chemotherapy with long-lasting effects.
- Matthew Dons discusses personalized cancer treatment costs in Japan, ranging from $25,000 to hundreds of thousands of dollars.

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TRANSCRIPT

Brian McCloskey
Welcome everybody to the Cancer Patient Lab.

Roger Royse 1:13
Today's presenter, Matthew Dons, is going to tell us all about a really interesting therapy in Japan. I met Matthew probably a year ago through a Facebook group. It was a long, circuitous way to get to them. I was very interested in immunotherapy at the time, and I was trying to find places that would offer it since we're in the US, and we have the FDA to deal with. Also some other other types of therapies beyond standard of care. That's when I came across Matthew’s Facebook group, where it describes the kind of stuff they do in Japan, such as NK cell expansion, and dendritic cell expansion. I've been there twice now this last year. I got all of the above plus some other things, but most importantly, the neoantigen peptide vaccine. I've gone on a parallel track. I've got that being produced here. Things just move at a snail's pace here because of FDA rules. We're able to do it for a fraction of the cost. You'll find Matthew's story to be really interesting. I'll let him tell you. I don't want to steal any of his thunder. But I can tell you that this has been really one of the cornerstones of my treatment. I'm really glad that I found it.

Matthew Dons 2:50
I'm going to briefly just tell my story, and talk a bit about how the treatment works.

But first, here is my website address, email address, and YouTube channel.

- My website https://www.makecancerhistory.jp/
- My email address: info@makecancerhistory.jp
- My Youtube channel: https://www.youtube.com/@makecancerhistory

Do email me if you want. Ask any questions, or if you want help coming to Japan to have the treatment that I've had.

My story starts in 2016. In July, I was 36, suddenly diagnosed with stage four colon cancer, a terminal cancer. At the time of diagnosis, it had spread to my abdominal membrane, the peritoneum. I didn't know we had an abdominal membrane. But apparently when your cancer is in the abdominal membrane, the prognosis is very poor. There's not very good blood supply to the tumors on the membrane. So chemo drugs don't get in. It's a bit like with brain cancer, where doctors talk about the blood-brain barrier. You have the same kind of situation with the peritoneum. Also It's difficult to see what's going on because tumors on the peritoneum don't show up well on scans. You tend to get lots of small tumors spread all over.

When I looked at the stats with standard treatment in 2016, in Europe at that time, colon cancer, even a stage four prognosis, was kind of okay. Well, okay, relatively speaking. After five years, maybe 10% of people are still alive. But if it spread to the abdominal membrane, that figure dropped to less than 1%. Around five years, you had like half a percent of people alive. That's based on five year survival data. So that would mean roughly data starting in 2011. Now we can

go back and recalculate that and see, in 2016 people in my situation, how long did they actually live? It turns out, instead of seven to nine months, it's closer to about 12 months, possibly 15 months. I'm talking about those who got successful treatment, like with surgery and chemo.

This was not good. I had two young kids. I thought it was probably a good idea to study oncology and find out if there were any options. So that's what I did. I'd been dividing my time between the UK and Japan, mainly Japan, for the previous eight years. So it was relatively straightforward, although I was diagnosed in the UK, to jump back on a plane, head back to Tokyo, and start treatment. That was because the standard care in Japan is much higher for cancer. It's probably just a few years ahead of the US, but maybe 10 years ahead of the UK.

Also, and this is an important point: in Japan, medical mistakes are very rare. In the US, if we believe the data, medical mistakes are the third biggest killer. The reason this is important in the context of cancer treatment is that often we're looking at treatments that give us a few percent advantage, or a combination of treatments that gives us a slightly bigger chance over standard care. So if you're in a country where care is very variable, or there's lots of mistakes, or in the UK, there are medical mistakes, but also a lot of waiting, that eats away that advantage. If you're in a place where there's a certain chance of your blood tests getting mixed up or being given the wrong drug or whatever, that's suddenly cut out that 10% advantage over standard care or whatever the you were getting.

I was just coming to have treatment in Japan because I knew the standard cancer care was very good here, expecting maybe I could hope to live a year with all the treatment. But what happened was, I had heard that the Japanese were doing this kind of immunotherapy that I'd read about in other places as well.

This is adoptive cell transfer immunotherapy. It's very different from the immunotherapy you've probably heard of in the media like the checkpoint inhibitors, like OPDIVO and Keytruda, that get a lot of media attention.

This is very different because this involves putting white blood cells in your body. In Japan, they use a combination of various kinds of white blood cells. I'll explain about those cells in a minute.

This is also different from CAR-T cell therapy, which you may have heard of. CAR-T cell therapy is also a type of adoptive cell transfer therapy. You're putting white blood cells into the blood. With CAR-T cell therapy, you are getting T-cells, a type of white blood cell. You are genetically engineering them to match the genetics of the patient's cancer, which is very good, because they're very highly targeted. However, there are a couple of issues. The issues are that your body has a high chance of reacting against the therapy, because there are foreign cells being put into you. T-cells are only able to attack cancer cells that are labeled as cancer cells. They're a type of white blood cell. The cells have to be labeled with an antigen or neoantigen.

Paul Van Camp (via chat):

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Please be specific as to what type of cancer and what stage. It makes a huge difference and cannot be generalized.

Matthew Dons 12:00
My cancer is stage four colon cancer, which spread to my abdominal membrane.

The whole point of this talk is that I'm talking about cancer-agnostic treatment. Cancer-agnostic treatment means a good response over all cancer types. This is very different from “tumor-agnostic treatment”, or it is sometimes called “tissue-agnostic treatment”. I'll explain those briefly because it is relevant.

“Tumor-agnostic treatment”, or so called “tissue-agnostic treatment” means treatment that is not matched to a specific cancer origin, like lung cancer, breast cancer, or bowel cancer. But “tumor-agnostic” means it's matched to a biomarker. There's typically going to be a protein that that cancer cell overexpresses.

I mentioned those checkpoint inhibitors like Keytruda. Keytruda was approved in the US in 2016 for skin cancer. Then in 2017, it was approved in the US for all tumor types, all cancer origins, if the patient has what's called “MSI high”, microsatellite instability high, which means the cancer is quite mutated. For those of you who are familiar with this, when you have stage four cancer, like me, the chance of being MSI high is very low – which makes sense if you think about it, because for early stage patients, if they have highly mutated cancer, it's very visible to the immune system, and likely to get a good immune response, likely to get a good treatment response, unlikely to go on to late stage cancer.

In my case, when my cancer was diagnosed, it was already stage four. First aid for colon cancer stage four, MSI high, is like 9%, something like that. Stage one colon cancer is considerably higher. There's a clear drop off. That drop off unfortunately corresponds to a poor prognosis.

I'm talking about treatment with a type of adoptive cell therapy, using various kinds of white blood cells, that seems to get a reasonable response over many, many cancer types; not matched to a specific genetic mutation, and not matched to a specific biomarker. I'll explain why that is, because that sounds a bit weird. As I mentioned, this is different from T-cell therapy. Although T-cells are one of the types of T-cell used. It is also different from CAR-T-cell therapy, where the cells being put in your body are bought from a pharmaceutical company. They're grown from a commercial cell line, and then genetically engineered for you. The cell therapy done in Japan, at least the one I had, is “autologous”. “Autologous” is a Latin term meaning “from your body” or “from the body”.

It's grown from your own white blood cells. From a patient's point of view, you go to the clinic, some blood is removed. If it's removed from your arm with a syringe, you can do some kinds of cell therapy, but not others, because just the number of the certain types of cells in your arm, in a 25 millimeter sample of blood, is very low. You can get the NK cells, which are one of the types of cells that are used here.

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The three types of cells used here are NK cells, T-cells, and dendritic cells. I'll explain the role of those very briefly.

The blood is removed by a process called “apheresis”. It is a little bit like kidney dialysis, like if someone goes to the hospital once or twice a week, or even has a dialysis machine at home. For apheresis, your blood is taken, but because you need quite a lot to get enough white blood cells, they return the blood that they don't need. The machine takes your blood. As it comes out into the machine it is put in a centrifuge and spun around.

Blood has four components: there's the red blood cells, the white blood cells, the plasma, and the platelets. All have different densities, which means when you spin it fast enough, it's going to separate out into the layers.

The apheresis machine in this case is set to drain away the white blood cells that it keeps, and then gives you back the rest of your blood. This takes about an hour or something from a patient's point of view. The number of white blood cells taken is a lot more than in a normal blood test. However, it's still a very small number compared to the number in your body. It's not like the process lessens your ability to fight cancer because you've got a load of white blood cells missing. Then comes three weeks of waiting while your cells are grown and selected and trained and incubated in the lab.

After three weeks they are returned to you, but a vastly bigger number, and the lab has selected the most cyto-active ones. With the T-cells, for example, the vast majority are not cytotoxic. Few of the .001% of T-cells are able to attack a cancer cell.

This treatment, as I said, uses three categories of white blood cells: NK cells, T-cells, and dendritic cells. Within those cell types there are different subtypes. Loads and loads of different T-cell subtypes have been identified.

T-cells attack cancer cells, and also viruses and bacteria. They can only attack labeled cells.

Dendritic cells look a bit like octopus cells. They float around the body and they look for foreign cells, and they will label them. They look for dead and damaged cells and they grab them and take them to the lymph nodes, where they meet up with the T-cells. Basically now the T-cells know what to go and find.

But the very, very big difference is NK cells are far, far more sophisticated white blood cells. They can attack cells that are not labeled as cancer cells, are not presenting an antigen, or not labeled with a neoantigen. This is very important for late stage patients, because they are able to attack cells that they recognize as being cancer, but not because of the labeling. As a late stage patient, many of the cancer cells that we have are these unlabeled ones.

Amit Gattani (in the chat) 20:37

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Many of the patients in this group are prostate cancer patients. That primarily spreads in the bone structure. When you say this works for all tumor types… Does this get to solid tumors in bones?

Matthew Dons 20:57
Bone mets are another reason why NK cells are good. The uptake in bone, either if it's a met from another cancer, or if it's a primary bone sarcoma, is good. In Japan, the response has been pretty good. NK cells do seem to cross the various barriers in the body, so good uptake if it spreads to the peritoneum. There's been a lot of stuff with using it for blocked primary brain cancer, but also brain mets as well. Results have been pretty good.

Paul Van Camp (via the chat)
For most immunotherapies advanced metastatic prostate cancer is considered “cold”, not responsive to most immunotherapies. The sole exception to date is an autologous dendritic cell therapy called Provenge (Sipuleucel-T) which is quite effective. Four months increase in mean survival in clinical trials, but greater than one year in real world experience.

Matthew Dons 22:19
On this idea of tumors being “hot” and “cold”: This is a term that you often see in marketing literature about hot tumors being very immune responsive and cold tumors not. In Japan the results do seem to be quite good using this mixture across all. For example, my tumor is MSS – microsatellite stable. The tumor mutational burden, which is also called “TMB,” is another measure of the mutation rate. Mine is quite low. My cancer when it was found was late stage, so probably quite a lot of immunosuppression. For people with the so-called cold tumors, it doesn't seem to be an issue.

The hot and cold thing is really when you're talking about immune checkpoint inhibitors. Checkpoint inhibitors are drugs that inhibit checkpoints. Immune checkpoints are things that stop the body's immune system from attacking cancer cells. Checkpoints are very, very important because they stop your immune system from attacking yourself. T-cells have a tendency to attack healthy tissue when overexcited. NK cells are very, very good at tissue discrimination. With the checkpoint inhibitors, the media often describe it as removing the brakes on the immune system, which is a good analogy. But what they don't say is that if you're a late stage patient, you have a very poor immune system, and removing the brakes doesn't generally help. That's why the checkpoint inhibitors give poor response for late stage patients. In the treatment I have in Japan, you're getting a huge, huge number of extra white blood cells put in your blood. It's like a billion to one ratio or something typically.

Roger Royse 24:34
With regards to checkpoint inhibitors in combination with this particular immunotherapy, I'm really worried about hyper progression. Because I've heard of that, and I've seen data all over the place, and I know of one patient who went to Japan who experienced it.

Matthew Dons 24:55

I'll explain hyper progression. First of all, hyper progression is a theory. It's a theory attached to these checkpoint inhibitors. Hyper progression is the idea that for some patients, they get a lot of hyper progression in their tumor growth after receiving an immune checkpoint inhibitor, like Keytruda or OPDIVO. This is a theory. All the immunotherapists I've talked to and a lot of the papers I've seen, say, “That's what it looks like, but that's probably not what's happening.” What's really happening is that what you had was just the timing, and there's just a lot of tumor progression at immunosuppression. When you think about the cancer, you've got your immune system, and cancer does immunosuppression. That means it generally weakens your immune system, particularly the number of white blood cells produced. That's one of the reasons why as cancer patients, we really struggle with infectious diseases and things like that.

Cancer also does what's called immune escape, which means it's specifically able to avoid the immune responses targeted at the cancer. Within those there are many, many mechanisms of immunosuppression. One that you may have heard of are T-regs, regulatory T-cells. Regulatory T-cells are a type of cell that limits the activity of T-cells so that the T-cells don't attack your body and kill you. You can measure that in a peripheral blood test. If the regulatory T-cells are very high, you can give a drug that will suppress them. Regular chemo suppresses them as well. You could do a couple of doses of chemo before the treatment to suppress them.

Roger, I've talked to a lot of immunotherapists, and I've spent a long time looking into the hyper progression thing. The immunotherapists that I've talked to believe that all you're really seeing is that the immunosuppression is winning, and it's not drug induced at all.

You must also be careful: there's this other term “pseudo progression”. In some cases, what you may be seeing is “pseudo progression”, where it looks like the cancer is getting worse, but isn't. This can be things like tumor growth. Sometimes a patient will have a certain type of immunotherapy. Immunotherapy is very, very wide. There are many types. The tumors may appear to get bigger. The proposed mechanism for this is that it's because a lot of white blood cells are rushing in there. Therefore the tumor is big on the scan. In the EU, they actually had to redo the protocols for clinical trials for immunotherapy drugs because what was happening was patients were getting immunotherapy when testing various kinds of immunotherapy. The trial endpoints were always progression free survival, which meant that when some patients were getting bigger tumors, they were then being kicked out of the trial and not monitored anymore. Years later, they were still doing okay, so this was pseudo progression. It's a very crowded issue, Roger, but the hyper progression thing is a theory associated with checkpoint inhibitors. It's not a theory that many immunotherapists seem to take seriously. It's far more, unfortunately, to do with a patient on a trajectory of immunosuppression, and that's what's happening.

Roger Royse 29:43
Maybe you could talk about NK expansion a little more?

Paul Van Camp (via the chat)
What is the specific drug/treatment and mechanism of activation of NK cells?

Matthew Dons 30:03
About the cell expansion: Expansion involves, first of all, selecting the more cytotoxic cells among the white blood cells taken from the patient, and then essentially, letting the cells breed and grow.

But also, there are lots of things you can do to make them more likely to find and kill the cancer cells. One thing that you can do is you may have a peptide protein available that matches well to that cancer patient's cancer type. You can incubate the dendritic cells with that.

That could be as general as: lots and lots of cancers produce this thing called “CA”. On your blood test you may track CA as a biomarker. A lot of cancers express that on the cell surface, and you can get a CA-targeted peptide. That's a commercial product that the immunotherapy lab is going to order from their supplier. They're using the incubation process.

Another thing you can do is incubate – this is not an either/or – there are various things you can do and many of them you can combine, and this is very much tailored to the patient.

You can do conditioning with heat shock proteins. When cancers are damaged, particularly by heat, or when all cells are damaged by heat, in fact, they get heat shock proteins forming on the surface. There are many, many kinds. They are categorized by their size, bizarrely, so that when you hear like a HSP 70, or HSP 90, that will be a 70 or 90 nanometer heat shock protein. This can be used to improve the process.

Dendritic cells only take about a week for optimal processing. NK cells take around three weeks for optimal processing. The way they're processed is important. On a very practical point, if you're going to do any kind of cell-based immunotherapy, my very, very, extremely strong recommendation is you only go to a clinic that does its own cell processing. The clinic should own a cell processing lab and be doing their own processing, so that they are being very kind of fanatical about the processing. You don't want your cells sent off somewhere, particularly sent across a border, for example. Because you may get some overzealous person at customs who opened up the package. See there's human cells, putting some bleach in cases of pathogens or whatever. In Europe, for example, there's a whole bunch of immunotherapy clinics that send cells to Greece for processing. I'm not going to comment on that specifically. What I would say, only go to the immunotherapy clinic that does its own processing.

Amit Gattani 34:07
You said what the growing process is. Is it personalized to the individual patient? What kind of biomarkers are checked for the individual patient? Can you talk a little bit about the personalization? What type of testing is required from a patient for that?

Matthew Dons 34:28
It's personalized, as much as possible, depending on the patient. That's evolving all the time as more and more peptides, for example, become available that are matched to certain biomarkers. This goes into also some of the other things that can be done to improve the

treatment that are not to do with the cell conditioning. The personalization, this is not like a full genome sequencing thing. It's very different from that, because remember, we're not talking about trying to target specific antigens. Because the problem with that is many, many of the cells are not presenting an antigen. Now you can, nowadays you can do neoantigen therapy as well. But again, many of the cancer cells, particularly for late stage patients are not presenting neoantigens, either. Neoantigens are like antigens that are appearing as part of the adaptive immune system, not innate, I believe. I'm not a doctor. I'm not an immunotherapist. As I've explained, some of the processing can be personalized. That can be essentially based on just the blood analysis that they do. The day before you do your apheresis, the lab is going to take a normal blood test. But In the lab, they're going to be mainly looking at white blood cell activity levels.

The measure for that is actually a bit crude. They get some white blood cells from you, they put them in a beaker with some cancer cells that have had a dye placed inside the cancer cells. There's an infrared sensor or an infrared source on either side of the device. It's not really a beaker. It is a bit more sophisticated than that. But as the white blood cells start attacking those cancer cells, the dye comes out, and less light passes through the light gate. So you can get a measure of how active the cells are. There's some kind of analysis that can be done.

This also feeds into what else you can do to make the treatment work a bit better. With colon cancer, for example, some of us are KRAS wild type, which means the cancer cells overexpress “epidermal growth factor receptor”, which is what makes your skin grow. Quite a few cancer cells overexpress that. That means you can use a targeted therapy called panitumumab or Erbitux. Cetuximab is the generic name. There's a pair of drugs. Cetuximab is only partially humanized. It's got mouse DNA in it, and that means your immune system recognizes it as being a little bit foreign.

Before the immunotherapy is administered to the patient, they can have a low dose of cetuximab (a targeted cancer drug used to treat advanced bowel cancer and head and neck cancers) and that will mark the cancer cells, and essentially it will act a bit like a neoantigen, making the cancer cells more visible to the T-cells.

A similar thing is Herceptin. Herceptin is a very famous cancer drug for breast cancer for HER-2 positive breast cancer. It turns out that quite a lot of cancers are also HER-2 over-expressive. In that case, Herceptin would be good. If the testing reveals that a targeted drug would be useful for you as a cancer patient, and that targeted drug is partially “humanized”, then it can be used to enhance this immunotherapy. (A drug is said to be “humanized” when its protein sequences have been modified to increase their similarity to those occurring naturally in humans.) In the case of the drugs I mentioned, panitumumab (a chemotherapy used to treat colon cancer) is fully humanized. So that wouldn't help you. It would be invisible.

Brian McCloskey 39:36
You have on here some veterans in cancer across a few different segments, who have seen several different treatments.

Do you have any sense of how multiple treatments can create heterogeneity of their cancers? How does this treatment work with patients who have seen multiple treatments?

Matthew Dons 40:10
There's this interesting thing, for example, about the hot and cold tumors. There's a lot of interest in, specifically for the checkpoint inhibitors, can you turn cold tumors into hot tumors? When we talk about these mechanisms, it's 100% guessing. You should be very, very skeptical of reports in the media where they're being very clear about this mechanism. This is all proposed guesswork. For example, with a patient where the cancer spread to the liver, and it's a so-called “cold tumor”, there have been good, not exactly preclinical results, treating those liver mets with radiofrequency ablation. This seems to then sensitize the cancer to checkpoint inhibitors. This research was done. There wasn't an animal study. It was a huge human study, but it was a human tissue study. It's using real tissue from real cancer patients. But it was a tissue study in a lab. The results are very, very promising. I heard about that a few years ago. I didn't hear anything after that.

There's so much interest at the moment with the checkpoint inhibitors because they are very commercial. You see a lot of these combo trials. Things like checkpoint inhibitors plus MEK inhibitors, seem to be getting some good results with that.

I’m very familiar with the colon cancer world. In colon cancer, late stage patients are about 10% or so MSI high and seem to naturally get a good response from checkpoint inhibitors. With some of those combination treatments, they're getting an extra 10 percentage points on that. They're getting like a 20% response. Unfortunately, for me, the extra 10% do not so far include patients where the cancer spread to the liver, which it has in my case. Maybe there are other mechanisms going on there.

Roger just made a comment about Japan being far less expensive, due to the FDA. I didn't personally know about the FDA there. But I do know that in some countries, cancer treatment is very, very expensive. In Japan, it's not. That's to do with how the Japanese health system is regulated. It's to do with the buying power of Japan, because there's a high population and a small space. Japanese people tend to live almost forever. There are a lot of elderly cancer patients. Japan has a lot of buying power.

Brian McCloskey 43:33
For cancer patients who have seen multiple treatments, what are the results of that, if there are any?

Matthew Dons 43:55
That's what I was trying to say about the hot and cold treatments. I have had a lot of cancer treatment. I strongly, strongly believe that I'm alive because of multiple treatments, especially multiple treatments at the same time, and especially choosing treatments that are not going to trash my immune system too much. So for example, in Japan with this, autologous adoptive cell therapy, the best results are always in conjunction with other treatments. For example, I've had

some of this immunotherapy in between chemo cycles, because in that situation, the chemo is wiping out some of your white blood cells, which generally is a very bad thing. In this case it can be a very good thing because then there's more tissue uptake. You're also wiping out some of those regulatory T-cells. When you have a treatment like chemo or radiotherapy that directly kills a lot of cancer cells, those dead and dying cancer cells are hanging in your body over a period of time. If you then have your dendritic cell therapy, there's just far more detritus floating around in your blood for the dendritic cells to find. Having this treatment just after radiotherapy, for example.

A treatment I've used a lot over the years is regional hyperthermia therapy. This is a treatment where you heat areas of the body. There seems to be a lot of immunotherapeutic effects from the heating. It seems to work particularly well with these three types of autologous therapy using T-cells, NK cells, and dendritic cells. There are lots of papers on that about proposed mechanisms. It is just guesswork. But part of it does seem to be to do with these heat shock proteins. When you heat tissue to like, so-called “fever temperatures”, like 41-42 degrees, something like that, over a sustained period of time, the cells get damaged. Part of the damage manifests as heat shock proteins on the surface of the cells. All the cells that are heated get damaged. It's not just the cancer cells, unfortunately. But as soon as the heat source is removed, within about 20 minutes, the self repair starts. But cancer cells are quite poor at self repair. So most of the cancer cells are still going to be covered in these heat shock proteins. There seems to be something that the immune system can recognize. Another benefit with hyperthermia therapy is that you get increased blood flow for about 24 hours into the area of the body that was heated. This enhances chemotherapy, for example, but particularly we want the injected immune cells to get where they need to go.

This is why you hear about certain immunotherapy clinics that are doing immunotherapy where they inject into the tumors getting very good results. But that's a very invasive process.

It doesn't seem to be done in Japan at the moment. The alternative the Japanese have come up with is to take dendritic cells and inject them in between your ribs because there's loads of lymph nodes there. This is extremely painful. The pain lasts for like a few seconds, but is extremely painful. But that seems to get good results without having to sedate the patient and inject right into the tumors, which of course, that's not going to be possible for many, many patients just because of where the tumors are located.

I have four pillars of how to get long-term survival from cancer:

6. Access the new treatments as quickly as possible. Do not wait for the approval. If the science seems sound, and early results seem good – go for it.
7. Combine treatments, particularly at the same time. This idea of like first line therapy, second line, third line therapy, that's an economic thing disguised as medicine, that's unfortunately, why we lose so many cancer patients.
8. Third thing which I really hate is having a lot of treatment. I've done a lot of treatment. That's why I've managed seven and a bit years now, not seven months of life. As much

treatment as your body can take, which kind of suggests you should try and choose the combination of gentler treatments.

9. Try to choose treatments that cause less immune suppression. Selecting the specifics really counts. If you're going to have radiotherapy, loads of different kinds of radiotherapy at the moment, you look at the papers which one seemed to cause the least bone marrow suppression. That's going to be like choosing something like TomoTherapy, or proton beam therapy, instead of the old school Linac (linear accelerator) therapy where with a blast, high dose of radiation, you're radiating all your bone mass.

Absolutely get multiple treatments, as much treatment as you can manage. I can't wait for the new treatments. I just have to access what's out there. Above all, I just see that all long-term survival comes from immune response, whether that's treatment-induced or some amazingly fortunate genetics.

You see this coming out again and again. When people talk about chemotherapy, where the papers are saying, “unusual response”, we believe this must have been a chemo-induced immune response. Why? Because the chemotherapy, yes, is suppressing your immune system. But also, it's killing a bunch of cancer cells, which means the immune system can see that, but you also reduce the immunosuppression because there are fewer cancer cells there to suppress the immune system.

Brian McCloskey 51:19
In your seven-year journey, when did you actually get this treatment? Like in year five or year six?

Matthew Dons 51:31
I first got this treatment just after my surgery, seven years ago. Because I'm in Japan, I've had this treatment several times spread out a small amount each time. That's for economic reasons, partly, but also because I'm an hour away from the clinic. When international patients come, the clinic is changing the protocol all the time based on results. But what they found tends to work well for international patients is to do like five days of treatment. Typically, on day one, you'd have your standard blood testing and some analysis. Day two, you'd have that apheresis process where the cells are collected. Then you've got your three weeks of waiting. You don't need to be in Japan for that, or don't need to be where the clinic is.

Although I should emphasize that international travel does take a lot of toll on your body, a lot more than we think. There are probably interesting mechanisms about that. But if you're ever considering treatment anywhere far away, please do consider that. International travel takes a big toll, and then coming back for like a week of treatments every day. I have not had a week of intensive treatment. I've had treatments spread over time.

Also, with the dendritic cell therapy, if frozen tumor tissue is available, this can be used. The tissue can be cut up, put with some conditioning stuff, and used to improve the conditioning of

the dendritic cells to be very, very highly targeted to your cancer cells. People get very, very confused because they think I'm talking about something that seems like neoantigen therapy. This is not that. This is not testing the tissue, doing a genome sequence, and then matching that to a neoantigen therapy. This is physically using the tumor tissue to condition the dendritic cells.

Last year, we saw an amazing result from that for primary brain cancer. This is a very, very hard thing to do a trial on because a surgeon is not going to agree to open you up just because you'd like some tumor tissue. This can't be done with pickled tumor tissue. It can't be done with something set in formaldehyde. You can use that for genetic testing. That's fantastic. But you can't use it for this. But there was a multicenter trial of primary brain cancer, and they got double the overall survival. This is for people with primary brain cancer where the prognosis is very, very poor and with a very, very small number of treatments available. The trial was just under a primary brain cancer, not because there was any belief it would work especially well for primary brain cancer. This is an agnostic treatment. It was because those patients have such a poor prognosis and so few treatments available. We expect that if you were able to do that kind of trial for other cancers, you'd get exactly the results. There doesn't seem to be any differentiation. A lot of this comes down to the sophistication of the white blood cells compared to a commercial immunotherapy product that's just targeting one thing and can't evolve and anything like that.

Amit Gattani 55:38
You talked about how heating kind of helps with immunotherapy. Similarly, other doctors use cryoablation when they do that. Does heating work better than cooling cryoablation?

Matthew Dons 56:03
I would like to make a general comment about cryoablation and the heating one – radiofrequency ablation. I'm not a doctor, and this is not medical advice, but it is absolutely criminal how underused these treatments are. Absolutely criminal. Forget about maybe they help with immunotherapy. Because from a patient's point of view, what is amazing about these treatments is we get multiple bites of the apple. If you have RFA (radio frequency ablation) or cryoablation, and you get a limited response or poor response, you can have it again. Yes, there are economic issues around that. If you have it, and you get no response, you then may still be able to go on and do the surgery.

As a general comment: it is absolutely disgusting that these treatments are not used as much as humanly possible. I will give a twenty-second anecdote: I had a lung tumor in my right lung. When I talked to the surgeon, he said he could take it out with a 100% chance of success, wedge resection, and a little keyhole surgery. The radiologist gave it about an 80% chance of success with TomoTherapy. Of course, the surgeon gave me a 100% chance. I said to the surgeon, “If I have this TomoTherapy, and it doesn't work, can you still do the surgery? And he can have undenied a bit and said, “Well, yeah, actually, that would still be no problem.” I went for the radiotherapy because it's far less invasive. In my case, it worked completely. But this was interesting, because it's an economic thing disguised as a medical thing.

Amit Gattani 58:02
Heat vs. cold. Are there data to say one works better than the other?

Matthew Dons 58:09
I have not seen it. I've looked around for comparisons.

A third one that is really worth looking into, if you can access it, is high HIFU, high-intensity focused ultrasound. This is meant to be a drop-in replacement for radiotherapy, just like RFA was. You're using high intensity ultrasound to ablate the tumors. Again, if you get a small response, you may have it multiple times. If it doesn't work, it hasn't suppressed your immune system. It hasn't trashed your liver, or whatever. You can go and have the other treatments. You can go and do your surgery.

Amit Gattani 59:00
Can you talk a little bit about the clinic that you and Roger have used?
How many doctors practice this?

Matthew Dons 59:12
I'm only familiar with literally the clinic that I've been to. I went there a lot because I went there every week for five years. Not for the immunotherapy – that would take more money than there is in the world, probably. But for the hyperthermia therapy, because for bizarre reasons I'm not going to go into, even though it's an experimental treatment, It's covered by Japanese national health insurance.

I can connect you to the clinic that I went to. My email address is above. The clinics and hospitals in Japan generally do not take international patients directly. You go through what's called “a medical travel assistance company”. This is the same for lots of Asian countries. I don't know outside of Asia. However, partly because I went there every week for five years, I can directly introduce patients, and if you're interested, I can set up an online consultation with a therapist there. This is a small clinic in Tokyo. They work with a network of other clinics.

One of the things they are involved in is metronomic chemotherapy, where you have a low dose of chemotherapy, but with no breaks, continuously. This has to be a tablet-based chemotherapy, and that seems to have a good immunotherapeutic effect. They work with a metronomic chemotherapy clinic. The doctor, the main immunotherapist who set up the clinic, Dr. Ted Anuma. He is the pioneer of immunotherapy in Japan. He seems to be the world leader for NK cell therapy. He was writing papers about certain aspects of it 10 years ago, and now the medical world is making a big fuss about the communication between NK cells and dendritic cells. NK cells seem to give a very surprisingly long response, like benefit over the years with dendritic cells. When you have dendritic cell therapy it seems that you get more T-cell activity for almost six months afterwards.

This is the kind of really long lasting effects we're talking about. It's not like they're the more drug-based immunotherapy where you get a big blast, and then in a long-term thing, you get the side effects. This is not that.

I have to say that this stuff is personalized, and therefore very expensive. Although I talked to a lot of American cancer patients. They're asking if I've missed off a zero, whatever, in the pricing. I'm not joking. Several have actually asked if there's a zero missing, because the standard, intensive treatment is going to be around $25,000. I'm British, where healthcare is free at the point of use. So it's very hard for me to understand paying for health treatment. Beyond my little brain, but apparently, in America you may pay hundreds of thousands of dollars. That $25,000 would be basic for the standard conditioning. There will be add on to that. An extra $1,000 for some kind of pre-treatment, for example. If you want them to store your cells for a year, so that you can come back and get some more, that might be another $1,000.

Amit Gattani 1:03:32
It's the same clinic that Roger has used. He has given me the contact information.

Matthew Dons 1:03:38
If you drop me an email, I can send you the patient questionnaire and stuff. If you want an online consultation, or any more details about practical points of coming to Japan. There's no need for a health treatment visa or anything like that. Generally you'd be in Tokyo for about four weeks.